Abstract# 2390

SOLID CANCERS IN SURVIVORS OF ALLOGENEIC BONE MARROW TRANSPLANTATION (BMT).

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We previously reported an increased risk of solid cancers in a large group of patients surviving more than 5y after BMT. That study had relatively few pts surviving >10 y postBMT. We have continued surveillance of these & other BMT survivors to determine whether solid cancer risk changed beyond 10y after transplantation. We assessed new cancers in 28,884 allogeneic BMT recipients & studied whether specific patient & transplant characteristics were associated with increased risk. 23,543 pts were transplanted from 1964-94 by 271 IBMTR teams with follow-up through 1995; 5341 pts were transplanted 1969-96 at FHCRC & followed through 1996. 6530 pts had survived ≥ 5y post-transplant, 1927 ≥ 10y, 367≥ 15y & 59 ≥ 20y. Transplantation was done predominantly for leukemia [acute & chronic myelogenous leukemia, acute lymphoblastic leukemia] (74%), aplastic anemia (10%), lymphoma (5%) & myelodysplastic syndromes (5%). Average age at transplantation was 27y (range <1-72y). 67% of pts received total body irradiation (TBI) as part of their preparative regimen. The cumulative incidence of invasive solid cancers for all pts was 2.2% ± 0.4% at 10y, 5.0% ± 1.2% at 15y, & 8.1% ± 3.1% at 20y. Compared to an age- & sex- matched general population, transplant recipients were at significantly higher risk of developing new invasive solid cancers [observed second cancers=161; observed/expected ratio (O/E)=2.3, (95%CI 1.93, 2.64)]. Risk increased with time since transplantation; the O/E ratio was 4.8 (3.2, 6.8) among 10y survivors. Sites with significantly ($p<0.05$) increased risks of second cancers after transplantation were oral cavity (O/E=11.6), salivary glands (O/E=14.2), liver (O/E=6.9), skin (O/E=4.2), brain (O/E=6.0), thyroid (O/E=6.3) & bone/connective tissue (O/E=8.4). A new finding in this study, not seen in previous reports, is a significantly increased risk of breast cancer among 10y survivors (O/E=3.3 with 5 observed cases). Univariate analyses of transplant related variables suggests that conditioning with TBI may increase the risk of subsequent cancers of the salivary, brain, thyroid, breast, bone/connective tissue & melanoma of the skin. Excess risk of solid cancers diminishes with increasing age at transplantation. These data indicate BMT survivors face increasing risks of solid cancers with time after transplantation, supporting lifelong surveillance.

Abstract# 2391

BUSULFAN (BU) - CYCLOPHOSPHAMIDE (CY) VERSUS CY-TOTAL BODY IRRADIATION AS CONDITIONING REGIMEN BEFORE BONE MARROW TRANSPLANTATION (BMT) FOR ACUTE MYELOGENOUS (AML) OR CHRONIC MYELOGNEOUS LEUKEMIA (CML) : LONG-TERM FOLLOW-UP OF THE 4 RANDOMIZED TRIALS.

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Background: In the early 90's 4 randomized trials comparing conditioning with Bu-Cy or Cy-TBI[1-4] were reported with follow-up ranging from 24 to 42 months. In 3 out 4 studies DFS rates were similar using either conditioning.

Aims: 1) to compare long-term survival, return to work, and general health status according to conditioning; 2) to estimate incidence rates and risk factors of late complications.

Methods: Cox regression models were fitted, stratified on trials.

Results: 305 patients (pts) with CML and 149 pts with AML were studied (follow-up > 7 years for surviving pts). In pts with AML 38% (Bu) and 28% (TBI) died (10-year survival 59.2% vs 69.5%, p = 0.4). In pts with CML 29% (Bu) and 28% (TBI) died (10-year survival rate of 69.4% vs 67.3%, p = 0.9). Most pts had either normal health status (WHO score = 0) or minimal impairment. 80% of the patient went back to work/school without difference using either conditioning (based on 160 patients; not available for the FHCRC trial). Cataract incidence was 12.3% vs 12.4% in AML (p = 0.82) and 16% vs 47% (p = 0.001) in CML pts receiving Bu-Cy or Cy-TBI, respectively. Risk factors associated with cataract included TBI (Hazard ratio (HR) 2.28, p=.0008) and CML (RR=3.32, p=.005). Late pulmonary disease occurred in 6% vs 6% in pts with AML and in 15% vs 15% of CML pts receiving Bu-Cy or Cy-TBI, respectively. Multivariable analysis found CML (HR=4.9, p=.002) and chronic GvHD (HR=3.1, p=.0007) as significant factors associated with this complication . Avascular osteonecrosis occurred in 6% vs 7% of pts with AML and in 3% vs 10% of CML pts receiving Bu-Cy or Cy-TBI, respectively. Multivariable analysis found younger age (HR=0.94, p=.002) and chronic GvHD (HR=6.35, p=.0009) as significant factors. Hypothyroidism (6 pts) and hyperthyroidism (1 case) were rarely reported. Persistent impairment of hair re-growth was assessable in 194 patients (data not available FHCRC) it occurred in 72%and 55% of the patients receiving Bu-Cy or Cy-TBI, respectively and was associated with chronic GvHD (OR=3, p=.01) and Bu (OR=2, p=.02).

References: [1] Blaise et al. Blood 79; 2578, [2] Devergie et al. Blood 85; 2263, [3] Clift et al. Blood 84; 2036, [4] Ringden et al Blood 83; 2273

Abstract# 2392

THE IMPACT OF PEDIATRIC MARROW TRANSPLANT (BMT) ON LATE PULMONARY FUNCTION.

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Chemotherapy and irradiation therapy may lead to chronic restrictive pulmonary disease (RPD) that is not manifest until years after initial treatment. In young children, lung and thoracic development may be impaired due to effects of chemoradiotherapy on growing lung tissue and bone. To determine the BMT preparative regimen effect on late pulmonary function (PF) in growing children, 182 patients who are currently >6 years (yr.) of age, ≥5 yr. after BMT and were <18 yrs. at BMT had PF tests performed. Preparative regimens were cyclophosphamide (CY) (N=18), busulfan + CY (N=27), CY + TBI 1.2 Gy x 12 (N=35), 2.0 Gy x 6-7 (N=36), 2.25 Gy x 7 (N=41), or 10.0 Gy (N=25). Donors were matched related (N=114), mismatched related (N=38), unrelated (N=21) or autologous (N=9). Patients were considered to have RPD if total lung capacity was less than 80% of predicted. The overall incidence of RPD was 26%. The univariate relative risks and multivariate adjusted p-values from variables significant in a multivariate analysis are shown in the table.

TBI Gy/fx		<0.001	**Chronic GVHD**		0.043
No TBI	—		No	—+	
1.2 Gy	0.61		Yes	1.54	
2.0 Gy	2.17				
2.25 Gy	3.02		**Diagnosis**		0.041
10.0 Gy	13.81		AA	—	
Yrs Dx - BMT		0.011	AML	0.44	
≤1	—		Non-Malig	1.00	
1 to 5	2.25		Solid Malig	1.20	
>5	6.75		ALL	2.22	

These data demonstrate that risk factors for RPD are TBI fractions of 10.0 Gy or 2.25 Gy, >5 yrs. from diagnosis to BMT, having chronic GVHD or ALL. Children <8 yrs. at BMT were as likely to develop RPD as those ≥8 yrs. (p=0.15). Acute GVHD did not impact development of RPD (p=0.89). Donor type was marginally significant in univariate (p=0.05) but not in multivariate analyses. Children receiving TBI regimens should have PF tests long-term after BMT to detect development of RPD.

AUTOGRAFTING: MULTIPLE MYELOMA

Abstract# 2393

SINGLE VERSUS DOUBLE TRANSPLANTATION IN MYELOMA: A PROSPECTIVE RANDOMIZED TRIAL OF THE INTER GROUPE FRANCOPHONE DU MYELOME (IFM).

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We previously reported that high dose therapy significantly improves overall survival in myeloma (IFM 90 trial). However, the 6-year EFS was only 24% after a single transplant. Promising results were reported after tandem transplants. The IFM initiated a randomized study to compare single versus double transplant.From October 94 to March 97, 402 untreated patients under the age of 60 years were randomized to receive a single autologous transplant(arm A) prepared with melphalan (140 mg/m2)and TBI (8Gy)or a double transplant (arm B)the first one prepared with melphalan (140 mg/m2)and the second one with melphalan (140 mg/m2)and TBI(8Gy).An intermediate analysis was performed on June 2OOO with a median follow-up of 4 years. Patients characteristics of each group (arm A=200 patients; arm B=202 patients)were similar and no significant difference was observed with regard to sex, age(52 years), stage DS, Ig isotype, beta-2microglobuline(4.7 mg/l),and CRP(13 mg/l).85% of patients could receive the first transplant and 78% in arm B could receive the second one (3 months after the first one). We observed 39% of CR or response >90% in arm A versus 49% in arm B (p=0.06). Median EFS and OS were comparable between the 2 treatment arms (arm A, 24 and 48 months; arm B, 30 and 54 months, respectively). In order to better appreciate the impact of the treatment arm on the long term survival , we analysed the subgroup of patients surviving more than 3 years after diagnosis (arm A, 100 patients; arm B, 98 patients). The initial characteristics of these 2 groups were similar. In these groups, double transplantation was found to significantly improve the 5-year post-diagnosis survival (70% versus 85%, p=0.01). Finally, double transplantation was not found to improve the median survival, but was found to improve the long term survival. A longer follow-up is still required to give definite conclusions.